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Research Progress on Surgical Step-Down Therapy for Early Breast Cancer

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Abstract

Breast cancer is one of the most common malignant tumors in women worldwide, posing a serious threat to women's health. The incidence of breast cancer is on the rise, and the proportion of early-stage breast cancer is also increasing. Breast cancer will account for 32% of all new cases in women in 2024, ranking first among all malignancies. Early-stage breast cancer refers to lesions that are confined to the breast and regional lymph nodes at the time of diagnosis without distant metastasis. Treatment strategies include neoadjuvant therapy before surgery, local treatment (surgery and/or radiotherapy), and adjuvant therapy after surgery. The purpose of the surgery is to completely remove the lesion while providing precise typing and staging to guide the systemic treatment strategy; neoadjuvant therapy downgrades the tumor, increases the chances of being operable, breast-preserving, and axillary-preserving, and assesses the sensitivity of the treatment to guide adjuvant intensive therapy; adjuvant therapy is classified based on the risk of disease recurrence for patients to improve their prognosis. This article reviews the expansion of indications and technical optimization for breast-conserving surgery, the progress of sentinel lymph node biopsy replacing axillary dissection, the role of neoadjuvant therapy in promoting surgical downgrading, and the application of artificial intelligence in treatment decision-making, and explores current challenges and future directions, aiming to provide references for clinical practice.

Keywords

Early-Stage Breast Cancer, Surgical Downgrading Therapy, Breast-Conserving Surgery, Sentinel Lymph Node Biopsy, Neoadjuvant Therapy, Artificial Intelligence

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1. Introduction

Breast cancer is the most common malignant tumor among women worldwide. There were 2.26 million new cases globally in 2020, and about 420,000 new cases in China each year. The detection rate of early-stage breast cancer (tumor diameter ≤ 5 cm, no distant metastasis, limited axillary lymph node metastasis) has been increasing year by year with the popularization of screening. Currently, the proportion of early-stage cases in China has reached more than 60%. Conventional treatment is centered on "maximum tolerable surgery". Radical surgery, although it can reduce the risk of recurrence, entails extensive surgical trauma and is prone to upper limb dysfunction, changes in appearance, etc., seriously affecting the quality of life of patients. Studies have shown that about 65 percent of patients undergoing radical surgery have varying degrees of psychological disorders and a significant decline in social engagement. Since the 1980s, landmark studies such as NSABP B-06 [1]. In the era of precision medicine, surgical downgrading therapy is centered on "precise assessment and individualized intervention". By integrating clinicopathological features, molecular typing, and prognostic markers, it reasonably reduces the scope of surgery while ensuring tumor control and combines systemic treatment (chemotherapy, endocrine therapy, targeted therapy) with local radiotherapy to achieve the goal of "equal emphasis on efficacy and quality of life". This article systematically reviews the key advancements in surgical step-down treatment for early breast cancer, including the optimization of surgical methods, the innovation of lymph node management strategies, the bridging role of neoadjuvant therapy, and the application of emerging technologies, providing a comprehensive reference for clinical practice.

2. Classification and Staging of Early Breast Cancer

2.1. Molecular Typing

Treatment strategies for early breast cancer depend on the typing and staging of early breast cancer. Based on gene expression profiles and immunohistochemical characteristics, early breast cancer can be classified into the following major molecular subtypes, with significant differences in biological behavior, treatment response, and prognosis among the subtypes. Breast cancer is further classified into hormone receptor-positive, triple-negative breast cancer (TNBC), and human epidermal growth factor receptor 2-positive type. Luminal A type: about 40% - 50% of early breast cancers, hormone receptor (ER and/or PR) positive, HER2 negative, with a low Ki-67 index (typically ≤ 14%). This subtype grows slowly, has low malignancy, is sensitive to endocrine therapy, has a good prognosis with a 5-year disease-free survival rate of over 90%, and is a major beneficiary of downgrading treatment. Luminal B type: accounting for 20% - 30%, it can be further divided into HER2-negative and HER2-positive subtypes. All are hormone receptor-positive and have a high Ki-67 index (>14%); HER2-positive subclasses are accompanied by HER2 overexpression or amplification. This subtype of tumor has high proliferative activity, and some may require combined

chemotherapy or targeted therapy. Downgrading therapy should be carefully evaluated in combination with tumor size and lymph node status. HER2-positive type: about 15% - 20%, hormone receptor-negative, HER2-positive. The tumor is highly aggressive, but with the use of targeted drugs such as trastuzumab and pertuzumab, the prognosis has improved significantly, and the pathological complete response (pCR) rate after neoadjuvant therapy can reach more than 60%, creating favorable conditions for surgical downgrading. Triple-negative type: 10% - 15% of cases, negative for both hormone receptor and HER2. Highly invasive, with a high risk of recurrence, and relatively sensitive to chemotherapy, with a neoadjuvant chemotherapy pCR rate of about 30% to 40%; those with pCR may consider downgrading surgery, but those without pCR require more aggressive local treatment [2].

2.2. Clinical Staging

The current breast cancer staging principles are based on the American Joint Committee on Cancer (AJCC) 8th edition breast cancer staging system (including traditional anatomical staging and prognostic staging). Stage 0 (Tis): carcinoma in situ, including ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS), is confined within the ducts or lobules, does not break through the basement membrane, and has no lymph node or distant metastasis. Stage IA: maximum diameter of the tumor ≤ 2 cm, no lymph node metastasis (T1N0M0); Stage IB: tumor with maximum diameter ≤ 2 cm and microlymph node metastasis (≤0.2 cm, T1N1miM0), or no evidence of primary tumor but microlymph node metastasis in the axillary area (T0N1miM0). Stage II: Stage IIA: tumor with a maximum diameter > 2 cm and ≤5 cm, no lymph node metastasis (T2N0M0); or tumor ≤ 2 cm with 1 - 3 lymph node metastases in the axillary area (T1N1M0); Stage IIB: tumor maximum diameter > 2 cm and ≤5 cm with 1 - 3 lymph node metastases in the axillary area (T2N1M0); or tumor > 5 cm but no lymph node metastasis (T3N0M0). The stage of early breast cancer directly affects the choice of treatment strategy. For example, patients with stage IA Luminal A type may be treated with breast-conserving surgery alone combined with endocrine therapy, while patients with stage IIB triple-negative may need neoadjuvant chemotherapy to determine the extent [2].

3. Local Treatment for Early-Stage Breast Cancer

3.1. Breast-Conserving Surgery and Precision Improvement

Breast-conserving surgery is a radical surgical treatment for breast cancer that aims to ensure no tumor residue while preserving as much normal breast tissue as possible. Fisher's 2002 study showed that there was no statistically [3]. LRR and overall survival among patients who underwent total mastectomy combined with breast-conserving radiotherapy. Therefore, breast-conserving surgery makes it possible to achieve minimal trauma to breast tissue and the greatest clinical benefit. In actual surgical procedures, the more tumor and surrounding normal breast

tissue are removed, the easier it is to achieve a negative margin, which contradicts the principle of "minimal damage", while a positive margin has a higher LRR, so an objective and standardized margin assessment method is particularly important. In 2014, the Society of Surgical Oncology (SSO) and the American Society for Therapeutic Radiology and Oncology (ASTRO) recommended that the criteria for negative margins in breast-conserving surgery should follow the "No ink on tumor" principle, which ensures that there is no tumor involvement at the margin. According to the 2016 American Society of Clinical Oncology (ASCO)-SSO-ASTRO consensus guideline, 2 mm is recommended as the standard for a negative margin in patients with DCIS. Since 2009, the "Chinese Anti-Cancer Association Guidelines and Specifications for the Diagnosis and Treatment of Breast Cancer (2024 Edition)" have recommended the use of ink staining to assess the margin, followed by formalin-fixed paraffin embedding, and the use of vertical margin radioactive sampling to observe and evaluate the position of tumor cells and margins in detail and completely to determine the margin for breast-preserving surgery. A retrospective analysis in the UK in 2022 conducted the largest meta-analysis [4] of the association between the margin of breast-saving surgery and disease metastasis and cancer survival. Of the 112,140 patients included in [5] the study, 9.4% had positive margins (with tumor involvement at the ink margin) and 17.8% had close margins (within 2 mm from the ink margin). Overall distant recurrence risk and local recurrence risk were higher in patients with positive margins than in those with close and negative margins—these combined data suggest that insufficient margin distance may lead to local and distant recurrence, as well as higher breast cancer mortality. Therefore, for invasive breast cancer or ductal carcinoma in situ, it is recommended that surgeons achieve a minimum tumor-free clear margin of at least 1 mm to improve patient prognosis [6]. It is currently believed that reducing the margin while preserving the natural shape of the breast as much as possible—even if there are a few cancer cells in the residual breast tissue after surgery—these lesions, through postoperative radiotherapy and systemic treatment, do not cause a higher ipsilateral breast recurrence rate or a higher risk of distant metastasis, which is the clinically acceptable outcome [5] of breast-conserving radical surgery. Breast-conserving surgical methods are also evolving, mainly including the following three surgical advancements: tumor plastic surgery techniques, through methods such as local gland flap metastasis and latissimus dorsi myocutaneous flap repair, the tissue defect after tumor resection can be effectively filled. For example, for tumors in the upper quadrant, the use of an "inverted T" incision combined with subfold glandular flap metastasis can significantly improve breast symmetry, with an excellent rate of cosmetic effect of 85% after surgery, which is 30% [7] higher than that of traditional breast-preserving surgery. Intraoperative electron beam radiotherapy (IOERT), which irradiates the tumor bed with a single dose of 20 Gy, can replace whole-breast radiotherapy six weeks after surgery. The ELIOT study showed that the 5-year local recurrence rate in the IOERT group (2.8%) was comparable to that in the total breast radiotherapy

group (3.0%), but the incidence of acute skin reactions (erythema, peeling) was reduced by 40%, and treatment compliance was significantly improved. 3D printing navigation technology: by reestablishing a three-dimensional model of the tumor through breast MRI before surgery and using 3D-printed personalized guides to assist in intraoperative positioning, the margin-positive rate can be reduced from 15% to 5.2%, and the rate of secondary surgery can be reduced by more than 60% [8].

3.2. Sentinel Lymph Node Biopsy (SLNB) for Breast Cancer

Sentinel lymph node biopsy (SLNB) replaces traditional axillary lymph node dissection (ALND) as the standard assessment method for clinically axillary-negative patients by identifying the "first stop" lymph nodes of tumor lymphatic drainage. Some patients have sequelae such as lymphedema, limb pain and numbness, and limited upper limb movement after ALND surgery, while the lymph node metastasis rate of all stages of breast cancer is only 40% to 50%. Therefore, routine ALND may cause 50% to 60% of patients to undergo unnecessary surgery [9]. The concept of the sentinel lymph node (SLN) emerged in 1960, defined as the regional lymph nodes in the primary tumor that receive lymphatic drainage first and have tumor cell metastasis first. The use of SLNB in patients with clinically negative lymph nodes in breast cancer undoubtedly avoids postoperative complications to a large extent and has no significant impact [9] on the prognosis of patients. For patients with clinically negative lymph nodes and SLNB-negative, global multicenter studies unanimously support exemption from ALND, with an axillary recurrence rate of only 0.6% 1.2% [10]. For example, a European registry study involving 5000 patients showed that the 5-year axillary recurrence risk for such patients was only 0.8%, without the need for further surgical intervention. With the widespread use of SLNB in clinical practice, the concept of further surgical downgrading treatment is also expanding the applicable population. First, for patients with axillary downstaging after neoadjuvant therapy, can the implementation of SLNB after neoadjuvant therapy accurately assess the pathological state of axillary lymph nodes and thus also provide an opportunity for exemption from ALND? Previous studies suggest that for patients evaluated as cN1 stage before neoadjuvant therapy, neoadjuvant therapy can turn lymph nodes negative in about 40% of patients, especially in TNBC or HER2-positive cN1 stage breast cancer patients, where about two-thirds of patients show no axillary lymph node metastasis after treatment. Three multicenter prospective clinical trials, ACOSOG Z1071, SENTINA, and SN FNAC, evaluated the feasibility and accuracy of SLNB in patients with initially positive axillary lymph nodes after neoadjuvant chemotherapy, and the results suggested that biopsy of ≥3 SLNs, double-tracer lymphangiography, and an axillary biopsy technique for marking metastatic lymph nodes before neoadjuvant therapy can effectively reduce the false-negative rate of SLNB after neoadjuvant therapy. Patients who

meet these conditions have a negative SLN after neoadjuvant therapy and can safely be exempted from ALND.

4. The Promotion of Surgical Downgrading by Neoadjuvant Therapy

4.1. Efficacy Prediction of Neoadjuvant Therapy and Surgical Decision-Making

Adjuvant therapy refers to systematic systemic treatment carried out after surgery. At present, the prognosis of patients with different subtypes of early breast cancer has improved significantly after treatment. A number of studies have shown good therapeutic outcomes for patients with breast cancer at medium to high risk of recurrence. Neoadjuvant therapy has become the standard treatment for locally advanced and some high-risk early-stage breast cancer by reducing tumor size and downstaging before surgery, creating conditions for surgical downgrading. The MonarchE study enrolled 5637 patients. The treatment group received adjuvant abeciclib combined with standard endocrine therapy regimens, with a median follow-up of 54 months. The results showed a 32% reduction in the risk of recurrence and 5 years of invasive disease-free survival (iDFS). The iDFS rate increased significantly compared to the control group (83.6% vs 76.0%). The NATALEE study further confirmed that among 5101 high-risk patients with positive or negative lymph nodes, 3-year adjuvant rebociclib reduced the risk of recurrence by 29% compared with conventional endocrine therapy, and the 4-year absolute benefit rate of iDFS was 4.9%;a team from Fudan University Shanghai Cancer Center conducted stratified treatment for TNBC patients and found that low-risk patients had a 3-year disease-free survival (DFS) rate of up to 90.1% after receiving conventional chemotherapy, while high-risk patients received anthracyclines and taxanes followed by an enhanced chemotherapy regimen of gemcitabine and platinum-based drugs. The 3-year disease-free survival rate reached 90.9%, significantly higher than 80.6% in the conventional chemotherapy group. The APHINITY study reported the follow-up of patients who received trastuzumab and pertuzumab in combination with chemotherapy after surgery. The results showed an 8-year iDFS rate of 86.1% in patients with positive axillary lymph nodes and 92.3% in patients with negative axillary lymph nodes. For high-risk HER2-negative early breast cancer patients with germline BRCA mutations, the Phase III randomized controlled clinical trial OlympiA confirmed that one year of olaparib adjuvant therapy could further reduce the risk of recurrence by 42%, and the 3-year iDFS rate increased from 77.0% to 85.9%. All of the above studies enrolled patients with clinically high-risk subtypes of early breast cancer. After optimized systemic adjuvant therapy, the overall prognosis improved significantly, which also laid the foundation [11] for the formation, promotion, and popularization of the surgical downgrading treatment concept. There are significant differences in response to neoadjuvant therapy among different molecular subtypes, and accurate prediction of efficacy is a prerequisite for surgical downgrading. For HER2-positive breast

[12] cancer: dual-targeted therapy with [13] trastuzumab combined with pertuzumab yields a pathological complete response (pCR) rate of 60% to 70% [13]. NeoSphere studies showed [14] that breast retention in pCR patients increased to 70%, and the 5-year disease-free survival rate reached 90%. Hormone receptor-positive breast cancer: 45% of postmenopausal patients who received neoadjuvant therapy with aromatase inhibitors (such as anastrozole) for six months experienced a tumor reduction of ≥50%, with a pCR rate of about 10% - 15%, but even without pCR, tumor regression still increases the chance of breast preservation. Triple-negative breast cancer: The PCR rate for neoadjuvant chemotherapy (such as the TC regimen) is about 30% to 40%, and the local recurrence rate 5 years after breast-conserving surgery for pCR patients is only 3.2%, significantly lower than that for non-PCR patients (8.5%).

4.2. Individualized Selection of the Surgical Range after Neoadjuvant Therapy

The "watch-and-wait" exploration for patients with clinical complete response (cCR) was for those who achieved cCR after neoadjuvant therapy (with no clinical or imaging evidence of tumor) with a pCR predictive value of ≥90%, and some studies attempted to exempt surgery. As shown in the I-SPY2 study subgroup, the 2-year local recurrence rate of HER2-positive cCR patients was approximately 3.1%, but this strategy still requires larger-scale studies for validation and is currently only recommended for clinical trials. The management after axillary lymph node downstaging refers to axillary-positive patients before neoadjuvant therapy. If it turns negative after treatment, the false-negative rate of SLNB re-evaluation is about 5%, and combined ultrasound or MRI evaluation can be reduced to less than 3%. As shown in the SENTINA study, the 5-year axillary recurrence rate of patients exempted from ALND was 1.5%, comparable to that of the ALND group (1.3%) [14]-[16]. At present, breast cancer has entered an era of individualized treatment based on molecular subtypes, and the choice of neoadjuvant therapy drugs also needs to be based on the patient's tumor burden and the expression levels of ER, PR, and HER2, as well as the Ki-67 proliferation index. From different perspectives, the advantages of neoadjuvant therapy include: 1) from the perspective of tumorigenesis and development mechanisms, neoadjuvant therapy enables earlier and more effective treatment of distant micrometastases of the tumor; preventing postoperative tumor recurrence and metastasis due to reduced angiogenesis inhibitors and an increased number of drug-resistant cells; 2) from a clinical perspective, neoadjuvant therapy downstages the primary lesion and regional lymph nodes of breast cancer, allowing tumors that were previously inoperable to be cured through neoadjuvant therapy; it gives patients who were previously unable to undergo breast-conserving surgery the opportunity to do so; to prevent axillary dissection (auxiliary lymph node dissection, ALND) for patients who would otherwise need axillary dissection after axillary downstaging; monitoring tumor sensitivity to treatment regimens provides a basis for the selection of post-

operative adjuvant therapy; 3) from a scientific perspective, neoadjuvant therapy provides a research platform to accelerate the discovery of biomarkers, establish indicators for predicting efficacy and biomarkers related to residual tumor or tumor drug resistance; testing the efficacy of new combination therapies can rapidly assess the efficacy of new drugs and accelerate the development of new anti-tumor drugs. Based on current evidence-based medical evidence, the effect of neoadjuvant therapy with the same regimen and course is the same as that of adjuvant therapy. If the treatment is effective and surgery is performed after completing the full course of neoadjuvant therapy without achieving pathologic complete remission, patients with pCR have the opportunity to use intensive treatment regimens to further reduce the risk of relapse and death [17]. In terms of TNBC, the KEYNOTE522 study showed that chemotherapy combined with pembrolizumab achieved a 64% pCR rate [18]. Similarly, in patients with HER2-positive breast cancer, the combination of taxane and platinum-based drugs with trastuzumab and pertuzumab yields a pCR rate of more than 60%, providing a broader exploration space for surgical downgrading, especially for local treatment downgrading after neoadjuvant therapy [12] [19].

5. Technological Innovation and Precise Evaluation System

Artificial intelligence (AI) provides quantitative decision support for downgrading treatment by integrating imaging, pathological, and molecular data. Deep learning models based on breast MRI can automatically identify the tumor invasion boundary and then evaluate the margin of breast-conserving surgery, achieving a positive margin prediction accuracy of 85%, which is 30% higher than manual assessment and reduces the rate of reoperation. The AI algorithm integrates clinicopathological features (age, tumor grade) and gene expression data to predict the risk of recurrence. It can predict the risk of recurrence 10 years after breast-conserving surgery with an accuracy rate of 88%, providing a basis for radiotherapy exemption (such as low-risk patients with Luminal A type). Sentinel lymph node metastasis can be predicted using an AI model that combines ultrasound images with clinical data, with an AUC value of 0.89 for the preoperative prediction of sentinel lymph node metastasis, screening out 20% of low-risk patients to avoid SLNB [20].

6. Summary and Outlook

In summary, surgical downgrading treatment for early breast cancer has entered an era of precision and individualization. The expansion of indications for breast-conserving surgery, the simplification of axillary lymph node management, and the application of neoadjuvant therapy have significantly reduced surgical trauma while ensuring treatment outcomes. With the precise classification of breast cancer treatment modalities, the emergence of new technologies, and the introduction of more highly effective and low-toxicity new drugs, systemic treatment strategies will continue to be optimized. While providing active and effective treatment

for patients with early-stage breast cancer, more consideration should be given to improving the quality of life of patients. At present, the treatment of early-stage breast cancer is becoming increasingly precise and refined, and the scope of surgical operations is constantly shrinking; with the advancement of various treatment techniques in the future, it is expected that the quality of life of patients will be further improved and more patients will benefit from it. In the future development of breast cancer treatment, individualized treatment guided by molecular typing will continue to be the basis, and the concept of systemic treatment step-up and local treatment step-down will be implemented. While reducing the risk of recurrence, the damage caused by treatment will be minimized as much as possible, and the pursuit of improving the long-term quality of life and prognosis of patients will be enhanced. More attention should be paid to the quality of life and rehabilitation care of breast cancer patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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